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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/800,629	03/07/2001	Nicholas M. Dean	ISPH-0537	8249

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EXAMINER
GIBBS, TERRA C

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/23/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/800,629	DEAN ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-23,28-54 and 67-72* is/are pending in the application.

4a) Of the above claim(s) *4-6,13,28-48,51-54 and 68-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7-12,14-23,49,50 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the Election filed February 21, in Paper No. 14 and to the Amendment filed November 14, 2002 in Paper No. 12.

Response to Amendment

Claims 3, 24-27 and 55-66 have been canceled. Claims 1, 5, 13, 21-23, 40, 49-54 and 67-72 have been amended.

Claims 4, 5, 6, 13, 28-48, 51-54 and 68-72 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (Election) requirement in Paper No. 14.

Claims 1, 2, 4-23, 28-54 and 67-72 are pending in the instant application.

Claims 1, 2, 7-12, 14-23, 49, 50 and 67 have been examined to the extent they read on the elected subject matter.

Election/Restrictions

Applicant's election with traverse of SEQ ID NO: 78, targeted to human interleukin-5 in Paper No. 15 is acknowledged. The traversal is on the ground(s) that all of the claims are related to the single concept of modulating interleukin-5 signal transduction. Further, Applicant argues that a search of literature relating to modulating interleukin-5 signal transduction would clearly reveal art relating to all of the claims, and therefore would not place an undue burden on the Examiner. This is not found persuasive because, as argued in the restriction requirement (Paper

No. 13), the antisense sequences claimed each target and modulate expression of different genes, namely interleukin-5 and interleukin-5 receptor a. Thus, the instant antisense sequences are considered to be unrelated, since each antisense sequence claimed is structurally and functionally independent and distinct. As further argued, a search of more than one (1) of the antisense sequences claimed presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed antisense sequences.

The requirement is still deemed proper and is therefore made FINAL.

Specification

The Amendment to the Specification to correct and complete the ATCC address is acknowledged.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The rejection of claims 49, 51, and 52 under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a away as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims is withdrawn (*in part*) in view of Applicant's arguments.

Applicants, in response to the previous Office Action, argue that the Examiner has failed to provide reasons for the rejection of claims 70-72 based on the cited references. Applicants

also argue that in effort to advance the prosecution of the case, Applicants have amended claims 49 and 51-52 to recite that the methods are performed *in vitro* and have canceled claims 55-66. Applicants further argue that claims 67-69 have been amended to remove the term "pharmaceutical". In view of the Amendments, the 35 U.S.C. 112, first paragraph rejection against claims 49 and 51-72, is hereby withdrawn.

The 35 U.S.C. 112, first paragraph rejection against claim 50 is maintained for the reasons of record, as set forth in the Office action mailed August 14, 2002.

Applicants, in response to the previous Office Action, argue that the articles cited regarding the unpredictability of the technology of antisense-based therapy actually teach the usefulness of antisense drugs in humans (see Branch, A. and Crooke, S.). Applicants further argue that the Specification as filed, at pages 60-64, supports results for using antisense compounds *in vivo*. Applicants also argue that eosinophilia was prevented in mice dosed *in vivo* with antisense oligonucleotides and interleukin-5 levels were decreased in mice after pretreatment with antisense compounds of the instant invention. Applicants further argue that the Specification as filed demonstrates that the compounds of the instant invention are pharmacologically active *in vivo* to reduce interleukin-5 levels and thus treat allergic asthma in an art-accepted animal model for human asthma.

Applicant's arguments have been fully considered, but are not found persuasive because as argued in the previous Office Action, the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome. Regarding Applicants arguments that the articles cited

regarding the unpredictability of the technology of antisense-based therapy actually teach the usefulness of antisense drugs in humans, this is not true. As a matter of fact, Branch discusses the studies of antisense therapies for chronic myeloid leukemia. Branch illustrates the potential of antisense therapies by citing a study with promising antisense inhibitory effects *in vivo*. However, Branch goes on to discuss that this same reference disappointingly reported a non-antisense mechanism was responsible for their own results (see page 46, last column).

Furthermore, regarding Applicant's art-accepted animal model for human asthma, Richards, I.M. (Clinical and Experimental Allergy, 1996 Vol. 26:618-620) assert that, "clearly all animal models of bronchopulmonary eosinophilia are not equal, and none of these are asthma. In our laboratories and elsewhere, murine models of antigen-induced lung eosinophilic inflammation have been developed which have many features in common with asthma, but as far as we know, none of these demonstrate an inflammatory pathology which is similar to that seen in the disease in man" (see page 619, last paragraph). Kumar et al. (Immunology and cell Biology, 2001 Vol. 79:141-144) assert that experimental models of acute allergic bronchopulmonary inflammation in mice are useful for the investigation of immunological mechanisms and of cellular recruitment, but have significant limitations because they fail to reproduce a number of characteristic lesions of human asthma, while usually being associated with marked alveolitis (see Abstract). Humbert et al. (Am. J. Respir. Crit. Care Med., 1997 Vol. 156:704-708) emphasize, "Since the precise mechanism of bronchial hyperreactivity in human asthma is unknown, it is difficult to assume that experimental manipulations that produce bronchial hyperactivity in animals, although arguably physiologically similar to that observed in humans, are also pathogenetically similar". The assertions of Richards and Kumar et al. indicate

that the current animal models for human asthma have significant limitations and are not an accurate representation of human asthma pathology. The emphasis by Humbert et al. indicates that it is difficult to assume that experimental manipulations of asthma in animal models are pathogenetically similar to humans.

In view of the unpredictability in the art of antisense-based therapy and the unpredictability of Applicant's animal model for human asthma, the specification as filed does not provide adequate guidance or examples that would show by correlation how one skilled in the art would practice the claimed invention over the scope claimed without having to engage in trial and error or undue experimentation.

The specification as filed contemplates the therapeutic use of interleukin-5 antisense in human asthma. However, the instant specification does not show any specific link between preventing eosinophilia in mice dosed with IL-5 antisense oligonucleotides such that treatment of asthma in a human with interleukin-5 antisense would be an apparent treatment option. It is unclear how the specific eosinophilia prevention data is correlated with/or representative of treatment of asthma in a human with any interleukin-5 antisense, especially in view of the references which illustrate that current animal models for human asthma are not representative of human asthma pathology (see Richards, I.M., Kumar et al., and Humbert et al.

The specification does not provide particular guidance or particular direction for the treatment of asthma with interleukin-5 antisense in a human. While the specification provides guidance to preventing eosinophilia in an ovalbumin-induced murine lung asthma model, the specification provides no particular nexus between the treatment of asthma in a human, as contemplated by the specification. The specification provides no particular guidance or direction

for the treatment of asthma in a human using the interleukin-5 antisense oligonucleotides of the claimed invention. Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art of antisense-based therapy and the unpredictability of Applicant's animal model for human asthma, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the claimed invention commensurate with the full scope of the claims. Due to the lack of specific guidance in the specification as filed and the lack of correlation between preventing eosinophilia in an ovalbumin-induced murine lung asthma model and treating asthma in a human, one of skill in the art would require specific guidance to practice the current invention. The current specification does not provide such guidance to treat asthma in a human and one of skill in the art would be required to perform trial and error or undue experimentation. The quantity of experimentation required to practice the invention over the scope claimed would include the de novo determination of how to engineer and deliver an antisense targeting interleukin-5 such that human asthma would be treated to any degree, particularly, in view of the obstacles needed to overcome to use antisense therapies as exemplified in the references discussed above.

Therefore, the 35 U.S.C. 112, first paragraph rejection against claim 50 is maintained for the reasons of record, as set forth in the Office action mailed August 14, 2002 in further view of Richards, Kumar et al. and Humbert et al.

The 35 U.S.C. 102(b) rejection against claim 3 as being anticipated by Weltman et al. [U.S. Patent No. 6,048,726] is moot in view of Applicant's Amendment and cancellation of claims.

The 35 U.S.C. 102(b) rejection against claims 1, 2, 7, 8, 49 and 50 as being anticipated by Weltman et al. [U.S. Patent No. 6,048,726] is withdrawn in view of Applicant's arguments.

The 35 U.S.C. 102(b) rejection against claims 5 and 51 as being anticipated by Nyce et al. (WO 96/40162) is moot in view of Applicant's Amendment.

The 35 U.S.C. 102(b) rejection against claims 13 and 40 as being anticipated by Bennett et al. [U.S. Patent No. 6,210,892] is moot in view of Applicant's Amendment.

The 35 U.S.C. 102(b) rejection against claim 4 as being anticipated by Dolgonov et al. [U.S. Patent No. 5,821,091] is moot in view of Applicant's Amendment.

The 35 U.S.C. 103(a) rejection against claim 3 as being unpatentable over Weltman et al. and further in view of Dolgonov et al. Sahasrabudhe et al. (1996), Baracchini et al. [U.S. Patent No. 5,801,154], and Fritz et al. (1997) is moot in view of Applicant's Amendment and cancellation of claims.

The 35 U.S.C. 103(a) rejection against claim 4 as being unpatentable over Weltman et al. and further in view of Dolgonov et al. Sahasrabudhe et al. (1996), Baracchini et al. [U.S. Patent No. 5,801,154], and Fritz et al. (1997) is moot in view of Applicant's Amendment.

The 35 U.S.C. 103(a) rejection against claim 13 as being unpatentable over Weltman et al. and further in view of Dolgonov et al. Sahasrabudhe et al. (1996), Baracchini et al. [U.S. Patent No. 5,801,154], and Fritz et al. (1997) is moot in view of Applicant's Amendment.

The 35 U.S.C. 103(a) rejection against claims 1, 2, 7-12, 14-23, 49 and 50 as being unpatentable over Weltman et al. and further in view of Dolgonov et al. Sahasrabudhe et al. (1996), Baracchini et al. [U.S. Patent No. 5,801,154], and Fritz et al. (1997) is maintained for the reasons of record, as set forth in the Office action mailed August 14, 2002.

Applicants, in response to the previous Office Action, argue that the claims (as amended) recite specific regions within the nucleobase sequence of human interleukin-5 and only one particular coding region sequence is taught in the primary reference of Weltman et al. Applicants also argue that Weltman et al. do not teach other regions of interleukin-5 other than the coding region and thus this patent fails to teach any of the specific sequences of the instant invention. Applicants also argue that Dolgonov et al. and Sahasrabudhe et al. fail to teach a specific sequence. Applicants further argue that Baracchinni et al. teach modifications to antisense oligonucleotides to enhance activity, but do not teach or suggest the use of antisense compounds targeted to specific regions of interleukin-5. Applicants further argue that Fritz et al. disclose cationic polystyrene nanoparticles as carrier systems for antisense compounds in

general, but do not teach or suggest the use of antisense compounds targeted to specific regions of interleukin-5.

Applicant's argument has been carefully considered but are not considered persuasive because as argued in the Office action mailed August 14, 2002, it would have been obvious to make antisense oligonucleotides encoding interleukin-5 since the prior art has asserted that it is of considerable interest to investigate the possible role of interleukin-5 in eosinophilic inflammation (Weltman et al.) and asthma in mammalian cells. As further argued, one of ordinary skill in the art would have been motivated and expected success in making antisense oligonucleotides encoding interleukin-5 since Weltman et al. explicitly taught an antisense oligonucleotide targeted to the coding region of interleukin-5 which modulates the expression of mammalian interleukin-5. As further argued, one of ordinary skill in the art would have been motivated to include a peptide nucleic acid which is conjugated to at least one end of antisense oligonucleotide since Sahasrabudhe et al. taught oligodeoxynucleotide-peptide conjugates complexed to an RNA hairpin loop favor high affinity of the conjugate for an RNA target. As further argued, one of ordinary skill in the art would have been motivated to modify antisense oligonucleotides and had a reasonable expectation of success since the prior art has taught the desirability of such oligonucleotides are often preferred over native forms because of enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases and the exhibition of high colloidal stability with low toxic side effects as required for biological experiments (Baracchini et al. and Fritz et al.).

Further, regarding a compound 8 to 30 nucleobases in length targeted to a 5'-untranslated region, a stop codon region, or a 3'-untranslated region of a nucleic acid encoding human

interleukin-5 of SEQ ID NO: 78, as now recited in amended claim 1 and Applicant's arguments that Weltman et al. do not teach other regions of interleukin-5 other than the coding region and Dolgovov et al, Sahasrabudhe et al., Baracchini et al and Fritz et al. do not teach the use of antisense compounds targeted to specific regions of interleukin-5, Baracchini et al. teach antisense oligonucleotides that can specifically hybridize with a 5'-untranslated region, a stop codon region, or a 3'-untranslated sequence of a target gene (see column 9, lines 6-67 and column 10, lines 1-25 and Table 1). Thus, one of ordinary skill in the art would have been motivated and expected success to make an antisense compound targeting a specific region such as the 3'-untranslated region of a nucleic acid molecule encoding human interleukin-5 because it is well known in the art to target different sites/regions within a gene for the oligonucleotide interaction to occur such that a desired effect (e.g., detection or modulation of expression of the protein) will result. It is noted that there is no evidence of record to show any such differences between the interleukin-5 sequence of Weltman et al. and SEQ ID NO: 78 of the instant invention that would have resulted in an artisan not being able to successfully design and use antisense oligonucleotides targeted to different sites/regions of interleukin-5 of SEQ ID NO: 78 of the instant invention.

The 35 U.S.C. 103(a) rejection against claims 1, 2, 5-23, 49 and 51 as being anticipated by Nyce et al., Bennett et al., Sahasrabudhe et al., Baracchini et al. and Fritz et al. is moot in view of Applicant's Amendment.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 7, 8, 14-23, 49, 50 and 67 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5-15, 26, 27 and 30 of U.S. Patent No. 6,136,603 (603'). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed antisense compounds encoding human interleukin-5 of SEQ ID NO: 78 and the methods of inhibiting interleukin-5 expression in cells of tissues would fully embrace the antisense compounds of 603' and methods of inhibition using said antisense compounds. For example, the broad scope of claim 1 of 603', an antisense compound 8 to 30 nucleobases in length targeted to a 5'-untranslated region, a 3'-untranslated region or a stop codon of a murine or human nucleic acid molecule encoding interleukin-5 and wherein said antisense compound modulates the expression of interleukin-5 encompasses the narrow scope of claim 1 of the instant invention, an antisense compound 8 to 30 nucleobases in length targeted to a 3'-untranslated region of a nucleic acid molecule encoding human interleukin-5 of SEQ ID NO: 78, wherein said antisense compound modulates murine or human interleukin-5.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 50 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 50 recites the limitation "claim 3" in line 4. There is insufficient antecedent basis for this limitation in the claim because claim 3 is canceled.

Claim Objections

Claim 1 and its depending claims 2, 7-12, 14-23, 49, 50 and 67 are objected to because claim 1 is partly drawn to a nonelected invention. Claim 1 should be amended to recite only the elected subject matter.

Conclusion

Claims 1, 2, 7-12, 14-23, 49, 50 and 67 remain rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
April 18, 2003

RAM R. SHUKLA, PH.D
PATENT EXAMINER